

### **Remarks**

After entry of the foregoing amendment, claims 26-36 and 38-47 are currently pending in this application. Claims 26-35 and 41-46 are withdrawn as directed to non-elected subject matter. Claim 36 is amended, claim 37 is cancelled and claim 47 is newly added. Support for the amendments to claim 36 can be found at least at page 2, lines 21-22 (numbering of ring), at least at page 11, lines 25-26 and at Example 10 (T as an amino acid residue), and at least at original page 6, lines 1-28 (amendments to R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub>). Support for new claim 47 can be found at least at page 6, lines 22-24).

### **Objections to the Specification**

The title is objected to as not being descriptive. Applicants have amended the title herein to read "Collections of Pyrrolobenzodiazepine Compounds". Applicants respectfully submit that this amendment is sufficiently descriptive and overcomes the objection. Applicants therefore request that the rejection be withdrawn.

### **Objections to the Claims**

Claim 36 are objected to due to an informality. Applicants have amended claim 36 to correct the typographical error, and therefore, request that the objection be withdrawn.

### **Rejections Under Section 112, Second Paragraph**

Claims 36-40 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention for two reasons. First, the phrase "and there is optionally a double bond between C1 and C2 or C2 and C3" was found to be vague and indefinite because it is unclear which carbons are C1, C2 and C3. Applicants have amended claim 36 to label C1, C2 and C3.

Second, the phrase "R<sub>9</sub> (if not H-(T)<sub>n</sub>-X'-Y-A)" was found to be vague and indefinite because it implies that R<sub>9</sub> could be H-(T)<sub>n</sub>-X'-Y-A and only R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> have been defined in this way. Applicants have amended claim 36 to redefine R<sub>9</sub>.

Applicants respectfully submit that the amendments to claim 36 have overcome the rejections under § 112, second paragraph, and request that the rejections be withdrawn.

### **Rejections Under Section 112, First Paragraph**

Claims 36-40 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Office action contends that the claims are directed to a broad genus of compound libraries that encompasses an infinite number of libraries. To address this concern, Applicants have amended claim 36 to indicate that T is an amino acid residue. Applicants have also narrowed the scope of R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub>.

The fundamental inquiry for determining compliance with the written description requirement is whether the specification conveys with reasonable clarity to those skilled in the art that the inventors had possession of the claimed invention as of the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Possession can be shown by describing the invention with all of its limitations using such descriptive means as words, structures, figures, diagram, and formulas. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The claims, as amended, are directed to libraries that contain the preferred embodiments for several of the substituents, including T, R<sub>3</sub>, R<sub>6</sub>, R<sub>8</sub> and R<sub>9</sub>. (See specification at p. 6 and p. 11). Thus, Applicants respectfully submit that the claims as amended fully satisfy the written description requirement as the specification conveys that the inventors had possession of the claimed invention at the time of filing.

### **Rejections Under Section 103**

Claims 36-40 stand rejected as being unpatentable over Bi et al. (*Biorg. & Med. Chem. Lett.*, 1996, 6(19), 2299-2300) in view of Lescrinier et al. (*Chem. Eur. J.* 1998, 4(3), 425-433) and Leber et al. (*J. Am. Chem. Soc.*, 1988, 110, 2992-2993) and Suggs et al. (*Tet. Lett.* 1985, 26(40), 4871-4874) and Gordon et al. (*J. Med. Chem.* 1994, 37(10), 1385-1401) and Gallop et al. (*J. Med. Chem.*, 1994, 37(9), 1233-1251).

The Office action cites Bi et al. as teaching building blocks for peptide and carbamate libraries. However, the Office action admits that Bi et al. only teaches a C=O at the C<sub>11</sub> position and fails to teach a C-S, C-O or C-NH bond at that position. Further, the Office action admits that Bi et al. fails to teach the use of a solid support at the N<sub>10</sub> position or a combinatorial unit at the R<sub>2</sub> position or the actual formation of a combinatorial library. The Office action attempts to fill the many deficiencies in the teachings of Bi et al. by citing to numerous secondary references – Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al.

A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143). Further, obviousness cannot be established by the use of hindsight combination to produce the claimed invention. *In re Fine*, 837 F.2d at 1075, 5 USPQ 2d at 1599-1600. The sheer number of references necessary to make the alleged obviousness rejection point toward the non-obviousness of the claimed libraries and the use of impermissible hindsight.

Applicants respectfully submit that none of the claims is *prima facie* obvious over the cited art because there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the references, nor is there a reasonable expectation of success. It is only with applicants' disclosure as a guide that one of ordinary skill would have been led to the claimed libraries. Such hindsight is clearly impermissible under any standard for determining obviousness.

The libraries of the present invention form pyrrolobenzodiazepines which have the ability to recognize and bind specific sequences of DNA once the compounds are cleaved from the solid support. (Specification at p. 1, lines 33-36). The presence of an imine bond between N10 and C11 in the pyrrolobenzodiazepines allows for binding to DNA. Bi et al. teaches compounds that are lactams, i.e. those that have an oxo substituent at the C11 position. Thus, the compounds of Bi et al. cannot form an imine bond between N10 and C11 due to the oxo substituent at C11.

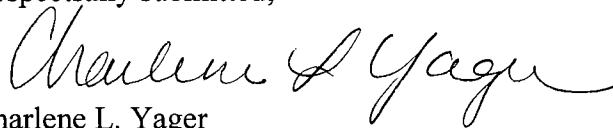
Lescrinier et al. teaches the formation of peptide-based libraries containing unnatural amino acids that can be screened for double-stranded DNA binding ligands. There is no teaching or suggestion in Lescrinier et al. regarding pyrrolobenzodiazepines. Gallop et al. and Gordon et al. are simply review articles discussing the application of combinatorial chemistry to drug discovery. They do not teach or suggest the pyrrolobenzodiazepine libraries of the present invention. Leber et al. merely discusses pyrrolobenzodiazepine antibiotics such as sibiromycin. It does not teach or suggest the formation of pyrrolobenzodiazepine libraries. Suggs et al. teaches a synthetic route to anathramycin (a pyrrolobenzodiazepine) analogs. It also does not teach or suggest the formation of pyrrolobenzodiazepine libraries.

Taken as a whole, the cited references do not teach or suggest the formation of pyrrolobenzodiazepine libraries in general, let alone the claimed pyrrolobenzodiazepine libraries. Thus, Applicants respectfully submit that the claimed invention is not obviousness and request that the rejection be withdrawn.

**CONCLUSION**

In view of the remarks presented herein, it is believed that this application is now in condition for allowance. The Examiner is strongly encouraged to contact the undersigned at the phone number below should any issues remain with respect to the application.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Charlene L. Yager".

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